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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/531,369	03/21/2000	Mark Williamson	07334-122001	6489

26161 7590 07/23/2003

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	26

DATE MAILED: 07/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/531,369	Williamson
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above, claim(s) *4-20* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3 and 21-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claim 22 has been amended. Claims 23-25 have been added. Claims 1-25 are pending. Claims 4-20, drawn to non-elected inventions, remain withdrawn from consideration. Claims 1-3, and 21-25 are under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The rejection of claims 1-3, 21 and 22 under 35 U.S.C. 102(e) as being anticipated by Fischer (US 6,071,696) as evidenced by Serrone et al (Melanoma Research, 1999, Vol. 9, pp. 51-58) is withdrawn in light of applicants arguments.

4. Claims 1-3 and 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Claims are rendered vague and indefinite in the recitation of MDA-9 as the only means of identifying the gene and protein on which the claimed methods depend. The use of laboratory designations only to identify proteins and genes upon which the claimed methods depend is vague and indefinite because different laboratories can use the same designation to identify completely different proteins and genes as well as using different designations to identify the same proteins and genes. Further, the metes and bounds of what constitutes a MDA-9 protein or gene has not been defined by the specification as it appears that the Accession Numbers and prior art citation on page 1, lines 25-27 may be by way of example rather than definition. Amendment of the Claims to recite a sequence identifier would overcome this rejection.

5. Claims 1-3 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is noted that the Claims have ben rejected for lacking a definition of MDA-9 that would define the metes and bound of the claimed protein(s) and gene(s) upon which the instant method Claims depend. Without a definition that would set the metes and bounds of what constitutes a MDA-9 protein or nucleic acid, it appears that the instant method Claims could be practiced with any gene or protein which is unregulated commensurate with drug-resistance and down regulated commensurate with lack of drug resistance. Accordingly, the Claims are lacking adequate written description for MDA-9. In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. In the instant case the functional activity of the MDA-9 protein as being diagnostic for drug resistance would be the only means to define a MDA-9 protein or gene. Thus, the instant method Claims encompass a genus of nucleic acids encoding proteins which are defined by functional activity, but not by structure. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "an adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties", not a mere "wish or plan for obtaining the claimed chemical invention". This is insufficient to support a method claim relying on a genus of nucleic acids encoding proteins. Because the genus of proteins and nucleic acids are not defined in terms of structure, it is concluded that the genus is highly variant as it encompasses species which have widely differing structural attributes. One of skill in the art would conclude that applicant did not disclose a representative number of species of the claimed genus, as a genus which tolerates widely different structural attributes would not be described by the prior art GenBank Accession Number AF006636, as stated on page 1.

Therefore, applicant was not in possession of the claimed genus of genes and proteins relied upon by the instant method Claims.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher (US 6,071,696) in view of the abstract of Stromskaya et al (Experimental and Toxicologic Pathology, 1995, Vol. 47, pp. 157-166) and Smith et al (The Journal of Biological Chemistry, 1995, Vol. 270, pp. 28145-28152). The specific embodiments of the instant claims have been recited in a previous action

Fisher teaches a method of identifying a compounds capable of elevating MDA-9 in cancer cells comprising incubating cancer cells with a test compound and measuring the expression of MDA-9 (column 9, lines 8-13). Fisher teaches the detection of MDA-9 levels as both the detection of MDA-9 mRNA (column 14, lines 16-29) and the detection of MDA-9 protein (column 10, lines 3-4) Fisher discloses MDA-9 as the melanoma differentiation associated gene which is an endogenous gene. Fisher teaches that the administration of IFN-beta with mezerein results in reduced MDA-9 expression with growth suppression as a result of terminal differentiation (column 2, lines 40-42). Fisher teaches that administration of interferons without mezerein to human melanoma cells results in the up regulation of MDA-9 commensurate with growth suppression (column 14, lines 59-62). Fisher does not teach the correlation between expression of MDA-9 and drug resistance.

Smith et al teach that mezerein is able to reverse drug resistance to the anti-cancer drug vinblastine (page 28148, second column, lines 22-24 and lines 30-36).

The abstracts of Stromskaya et al teach a correlation between the degree of differentiation and the degree of drug resistance in tumor cell populations.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to correlate the expression of MDA-9, as determined by the methods taught by Fisher with the drug sensitivity of tumor cells. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Smith et al regarding the ability of mezerein to reverse drug resistance, and the teachings of Stromskaya et al on the relationship between differentiation and multidrug resistance exhibited by tumor cells. One of skill in the art would conclude that a population of cells receiving Interferons only would be more differentiated and thus more drug resistance whereas the population of cells receiving the IFN-beta and mezerein were differentiated, but drug sensitive due to the presence of the mezerein. Thus, one of skill in the art would conclude that the observed MDA-9 levels were indicative of he degree of drug resistance in the cells.

8. Claims 1-3, 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher (US 6,071,696) in view of the abstract of Stromskaya et al (Experimental and Toxicologic Pathology, 1995, Vol. 47, pp. 157-166) and Smith et al (The Journal of biological Chemistry, 1995, Vol. 270, pp. 28145-28152) as applied to Claims 1-3, 21 and 22 above, and further in view of what is well known in the art as exemplified by the abstracts of Zamboni et al (Clinical Cancer Research, 1998, Vol..4, pp. 743-753) and Zhou et al (Drugs, 1992, Vol. 44, suppl. 4, pages 1-16).

The teachings of Fisher and Stromskaya et al and Smith et al as applied to the specific embodiments of Claims 1-3 , 21 and 22 are set froth above.

Claim 23 is drawn to a method for determining whether a test compound is a candidate modulator of the drug resistance of a cell, the method comprising determining the level of MDA-9 expression in a cell in the presence or absence of a test compound, selecting a compound as a candidate modulator of drug resistance if the levels of expression of MDA-9 in the presence of

the test compound differs from the level in the absence of the test compound, administering the selected test compound to a non-human mammal having drug resistant cells, determining whether the candidate modulator of drug resistance alters the drug resistance of the cells in the non-human mammal and identifying the candidate modulator of drug resistance as a modulator of drug resistance of the cell if the candidate compound alters the drug resistance of the cell in the non-human mammal. Claim 24 embodies the method of claim 23 wherein the level of MDA-9 expression is determined by measuring the level of mRNA encoding MDA-9. Claim 25 embodies the method of claim 23 wherein the level of MDA-9 expression is determined by measuring the level of MDA-9 protein.

The combination of Fisher and Stromskaya et al and Smith et al render obvious the specific embodiment of claim 23 with respect to sections a, b and c, for the reasons set forth above. None of the references specifically teach the administration of a candidate modulator of drug resistance to a non-human mammal as a means of identifying a modulator of drug resistance which alters the drug resistance of cells within a mammal.

It is well known in the art that drugs for clinical applications are tested in pre-clinical trials using animals. For instance, the abstract of Zamboni et al teaches that the compound Irinotecan which is toxic to human colon adenocarcinoma cells was tested in mice carrying human tumor xenografts. The abstract of Zhou et al teaches that the pharmacology of vinca alkaloids which are toxic to human cancer cells were tested in preclinical studies involving animals.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to test the candidate modulators of drug resistance in pre-clinical studies using mice carrying human tumor xenografts in order to determine efficacy of treatment, pharmakinetics and toxicology of the candidate modulator. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of both

the abstract of Zamboni et al and the abstract of Zhou et al exemplifying that such testing is routine in the art.

9. All other rejections and objections as set forth in Paper No. 15 are withdrawn.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

July 16, 2003